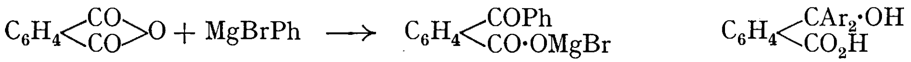
324. *Grignard Reactions with Phthalic Anhydrides.*

By Chaim Weizmann, Ernst Bergmann, and Felix Bergmann.

The usual synthesis of substituted benzoylbenzoic acids (and anthraquinones) from phthalic anhydrides, aromatic hydrocarbons (or derivatives), and aluminium chloride is not free from disadvantages: the position in which the second component links with the anhydride is not certain *a priori*; several simultaneous reactions may occur; and the aluminium chloride may totally or partly demethylate methoxyl groups or may even cause intramolecular rearrangement.

A less ambiguous method seemed to be indicated by Weizmann and Pickles's observation (P., 1904, **20**, 201) that phthalic anhydride reacts with phenyl- or α-naphthylmagnesium bromide to give *o*-benzoyl- or *o*-α-naphthoyl-benzoic acid:



$$\mathrm{C_6H_4}{<}\genfrac{}{}{0pt}{}{\mathrm{CO}}{\mathrm{CO}}{>}\mathrm{O} + \mathrm{MgBrPh} \longrightarrow \mathrm{C_6H_4}{<}\genfrac{}{}{0pt}{}{\mathrm{COPh}}{\mathrm{CO{\cdot}OMgBr}} \qquad \mathrm{C_6H_4}{<}\genfrac{}{}{0pt}{}{\mathrm{CAr_2{\cdot}OH}}{\mathrm{CO_2H}} \quad \text{(I.)}$$

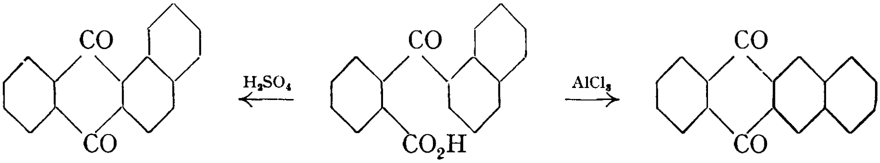
Here the position in which the anhydride molecule enters is determined by the position of the MgBr group, and no subsidiary reaction would be expected. There is, however, the possibility that the keto-acid salt reacts further with the Grignard compound to give a hydroxy-acid (I) or its lactone, but that can usually be prevented by using excess of the phthalic anhydride, *i.e.*, by adding the Grignard solution to the anhydride. Our experiments indicate that the tendency for further reaction is largely influenced by substituents, but this aspect was not pursued.

Our results for 16 reactions of this type are tabulated on p. 1369. Some of the resulting keto-acids had already been prepared by other methods; *e.g.*, Waldmann and Mathiowetz (*Ber.*, 1931, **64**, 1713), by condensation of naphthalene with naphthalene-2 : 3-dicarboxylic anhydride, had obtained a mixture of 2-α- and 2-β-naphthoyl-3-naphthoic acid, which was converted into a mixture of 1 : 2 : 6 : 7- and 2 : 3 : 6 : 7-dibenzanthraquinones. Our method, however, gives either the α- or the β-compound in a state of purity.

The condensation between phthalic anhydride (or acid) and phenanthrene by means of aluminium chloride has been described by Heller (*Ber.*, 1912, **45**, 670; compare Clar, *Ber.*, 1929, **62**, 350) and by Hoechster Farbwerke (D.R.-P. 194,328) as giving an amorphous mass or a yellow powder, m. p. 115°; but these products were obviously not identical with our well-crystallised *o*-9-phenanthroylbenzoic acid. The aluminium chloride probably facilitated substitution in a second position (cf. Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704). In these cases the Grignard method of synthesis is apparently superior to the usual one. Cyclisations similar to the above may be effected easily from all the benzoylbenzoic acids.

Some of the complex systems are sulphonated so easily that it is difficult or impossible to obtain quinones by means of concentrated sulphuric acid, even under mild conditions. That effect is especially marked in the case of *o*-9-phenanthroylbenzoic acid (see Graebe and Peter, *Annalen*, 1905, **340**, 259).

Apparently the course of the ring closure depends on the experimental conditions. The cyclisation of 2-α-naphthoylbenzoic acid with concentrated sulphuric acid leads to 1 : 2-benzanthraquinone (Weizmann and Pickles, *loc. cit.*), but use of a mixture of aluminium and sodium chlorides leads to naphthacenequinone (2 : 3-benzanthraquinone), owing to an intramolecular rearrangement (compare, *e.g.*, I. G. Farbenind., D.R.-P. 491,973; Scholl and Tritsch, *Monatsh.*, 1911, **32**, 997).



While this investigation was proceeding, Komppa and Rohrmann (*Annalen*, 1934, **509**, 259) described experiments on the interaction between aliphatic dicarboxylic acid anhydrides and Grignard compounds. Their assumption that Grignard compounds of high molecular weight give keto-acids and not diarylphthalides does not seem justified in view of the formation of di-α-naphthylphthalide, and the alleged connection between the nature of the product formed and the stability of the anhydride ring does not seem to be borne out by the facts. It has been assumed that, if the ring is opened easily, the keto-acid is formed; otherwise, the diarylphthalide is obtained. It is very improbable that the latter is formed by direct substitution of two aryl groups for one oxygen atom; we think that the keto-acid or its bromo-magnesium salt must be the intermediate product in the formation of the diarylphthalide. The former takes up a further molecule of the Grignard compound, and the hydroxy-acid is spontaneously converted into its lactone. That in keto-acid derivatives the keto-group reacts in preference to the acid group with Grignard reagents, is well known (compare Grignard, *Ann. Chim.*, 1902, **27**, 548).

EXPERIMENTAL.

Our results are summarised in the table. The keto-acids which are not italicised are recorded by Beilstein (Vol. X), except the last, which is described by Waldmann and Mathiowetz (*loc. cit.*).

Initial Materials.—Phthalic and tetrachlorophthalic anhydrides were commercial samples; for a gift of 2 : 3-naphthalenedicarboxylic anhydride (which we recrystallised from xylene) we are indebted to Dr. Wyler of the Imperial Chemical Industries. 4-Methoxyphthalic anhydride was prepared from commercial 4-hydroxyphthalic acid as follows : the acid was heated to 210° first at ordinary pressure and then in a vacuum (1 hour each), and the resulting anhydride distilled (b. p. 250—255°/25 mm.); it crystallised immediately, and was methylated (with cooling) by an ethereal solution of diazomethane (excess), the ether was evaporated, and the residue distilled under 25 mm. (b. p. 202°), and recrystallised from benzene–petroleum (1 : 1); m. p. 97°.

Details of Reaction.—The interaction of the anhydrides with Grignard compounds was usually carried out as follows. The anhydride was dissolved or suspended in boiling benzene or warm di-*n*-butyl ether on the water-bath, and the Grignard solution (10% excess) slowly added through a dropping funnel. The mixture was then boiled for 2 hours, decomposed with ice and sulphuric acid, the upper layer extracted with sodium carbonate solution, and the alkaline extract acidified, the keto-acid being thus obtained.

Sometimes part of the diarylphthalide is retained as the sodium salt of the corresponding hydroxy-acid in the alkaline extract and is recovered on acidification; but in this event, a further quantity of the same product is always obtained from the extracted ether–benzene layer. The yields were 70—80%.

Cyclisation of 2-α-Naphthoylbenzoic Acid.—The acid (1 g.) was heated at 140° for 1 hr. with anhydrous aluminium chloride (10 g.) and sodium chloride (2 g.). To the greenish mass, water was added at room temperature, and the solid product filtered off, washed with sodium carbonate

Anhydride.	Grignard compound.	Compound formed.	M. p.	Analysis, %. Calc. C.	Calc. H.	Found. C.	Found. H.	Colour reaction with H_2SO_4.	Remarks.
Phthalic	α-Bromonaphthalene	*o*-α-Naphthoylbenzoic acid	172°	—	—	—	—		From propyl alcohol; prisms
,,	β-Bromonaphthalene	o-β-*Naphthoylbenzoic acid*	128 (decomp.) as hydrate,	75·8	4·3	75·7	4·8		From butyl acetate; stout prisms
,,		*Di-β-naphthoylphthalide*	168 anhydrous	87·0	4·7	86·9	4·9		From methyl ethyl ketone or butyl acetate; clusters of lancet-shaped needles
,,	2-Bromo-6-methoxynaphthalene	o-(6-*Methoxy*-2-*naphthoyl*)*benzoic acid*	166	74·5	4·6	74·3	4·8	Violet-blue	From toluene; leaflets
,,	*p*-Bromoanisole	*o*-4-Methoxybenzoylbenzoic acid	148	—	—	—	—		From acetic acid (50%); needles
,,	*p*-Dibromobenzene	*o*-4-Bromobenzoylbenzoic acid	163	55·1	2·9	55·0	2·7		From toluene–ligroin
,,	9-Bromophenanthrene	o-9-*Phenanthroylbenzoic acid*	174—175	81·0	4·3	80·4	4·5	Violet-blue	From xylene; dimorphous: white clusters of needles, or clear yellowish prisms
4-Methoxyphthalic	Bromobenzene	4(5 ?)-*Methoxy*-2-*benzoylbenzoic acid*	167	70·3	4·7	69·8	4·8	Orange-red	From acetic acid (50%); needles
,,	α-Bromonaphthalene	4(5 ?)-*Methoxy*-2-α-*naphthoylbenzoic acid*	196	74·5	4·6	74·0	4·7	Purple-blue	From glacial acetic acid; prisms
Tetrachlorophthalic	Bromobenzene	Tetrachloro-*o*-benzoylbenzoic acid	188—189	46·1	1·7	45·1	1·9		From acetic acid (80%) or benzene; needles *
,,	α-Bromonaphthalene	Tetrachloro-*o*-α-naphthoylbenzoic acid	223 monohydrate	50·0	2·3	50·3	2·2		From acetic acid (80%); needles
,,	*p*-Bromoanisole	*Tetrachloro*-o-4-*anisoylbenzoic acid*	186—187	45·9	2·0	45·8	2·2	Orange-red	From glacial acetic acid or toluene; prisms
,,	*p*-Dibromobenzene	*Tetrachlorodi*-4-*bromophenylphthalide*	144—145 (decomp.)	41·2	1·4	40·3	1·8		From benzene or acetic acid (60%) *
Naphthalene-2 : 3-dicarboxylic	Bromobenzene	2-Benzoyl-3-naphthoic acid	205	—	—	—	—	Purple-red	From xylene
,,	α-Bromonaphthalene	2-α-*Naphthoyl*-3-*naphthoic acid*	228—229	81·0	4·3	80·8	4·5	First dark green, then dark blue	From propyl alcohol
,,	β-Bromonaphthalene	2-β-*Naphthoyl*-3-*naphthoic acid*	240	81·0	4·3	80·9	4·6		From butyl acetate; clusters of silky needles
,,	*p*-Bromoanisole	2-4′-*Methoxybenzoyl*-3-*naphthoic acid*	234	74·5	4·6	74·3	4·5		From glacial acetic acid; dimorphous: white, turbid or yellow, clear crystals

* The high halogen content makes this substance very difficultly combustible.

solution, then with water, and dried. With concentrated sulphuric acid, it gave an intense dark-violet colour. The product, on recrystallisation from nitrobenzene or amyl alcohol, gave 0·75 g. of pure naphthacenequinone (2 : 3-benzanthraquinone) (m. p. 276°); the mother-liquors also gave the above colour reaction, whereas the isomeric 1 : 2-benzanthraquinone (m. p. 168°) exhibits a beautiful green colour.

Cyclisation of 2-α-*Naphthoyl*-3-*naphthoic Acid*.—The acid (2 g.) was kept at 30° with concentrated sulphuric acid (20 c.c.) for 24 hrs., the mass poured into water, and the precipitate isolated by centrifuging, and washed with sodium carbonate and water. From glacial acetic acid, the 1 : 2 : 6 : 7-dibenzanthraquinone formed needles, m. p. 227°.

(Added in proof.) For the condensation of naphthalene with phthalic anhydride, see Underwood and Walsh, *J. Amer. Chem. Soc.*, 1935, **57**, 940; Barnett and Campbell, this vol., p. 1031.

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